12/18/04 Interim Review

VIOXX (rofecoxib)

Review of NDA 21042/s030 (Update of Cardiovascular thrombotic events in Alzheimer's studies 078 and 091)

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Disclaimer: This is a preliminary review of data submitted March 30, 2004. Corroboration of tables against patient listings, case report tabulations and case report forms has not been conducted yet. Several requests for clarification and for additional analyses are pending at the time of this review.

1) Background

NDA 21-042 was approved in May 1999 for the treatment of the signs and symptoms of OA, acute pain and dysmenorrhea. In year 2000, a large post-marketing outcome study (VIGOR) showed that the risk of serious GI complications was halved but the risk of cardiovascular thrombotic (CV/T) events was double for Vioxx 50 mg as compared to naproxen. Because of the study design, generalization of the study findings to other populations (such as those patients taking low dose aspirin), lower doses of Vioxx, and other non-selective NSAIDs comparators was not possible. At the risk of oversimplifying the picture, potential explanations to these findings were a plausible pro-thrombotic effect of Vioxx (unopposed inhibition of prostacyclins), sustained anti-platelet effects of naproxen, or a combination of both. Additional studies consistently showed a trend for higher CV/T events against Vioxx 25 mg as compared to naproxen. However, available data from placebo-controlled studies for the prevention of Alzheimer's disease did not suggest an excess of CV/T events for Vioxx. Labeling changes to include data from VIGOR and preliminary data from the Alzheimer's studies were implemented in April, 2002. The current submission of March 30, 2004 provided for an update of CV/T events included in the Precautions, CV effects, section of the Vioxx label. Before the review of this submission was completed, in September 30, 2004 results of a placebo-controlled study for the prevention of colonic polyps (APPROVe) lead to the withdrawal of Vioxx from the market.

Summary of Alzheimer's studies

Protocol 091 was a placebo-controlled, parallel-group, multicenter, 15-month double-blind study to evaluate the efficacy and safety of rofecoxib 25 mg to slow the progression of symptoms of Alzheimer's Disease. Patients of either gender who were ≥50 years of age with established, *possible or probable* Alzheimer's Disease were eligible to participate. Patients using NSAIDs for ≥7 days/month for the 2 months immediately prior to entry were not eligible. Patients were excluded if they were living

in a nursing home or skilled nursing facility. Eligible patients were randomized to rofecoxib 25 mg or placebo for 12 months. This was followed by an additional 3-month treatment phase in which 90% of the patients initially assigned to rofecoxib were treated with placebo while the other patients remained on their initial treatment. Safety and tolerability were assessed at each visit (screening, Months 1, 3, 6, 9, 12, 13.5, and 15). At the time of the Safety Update Report (SUR)(July 12, 2001) this study had been completed and had not shown efficacy.

Protocol 078 was a placebo-controlled, parallel-group, double-blind, multi-center study to evaluate the effects of rofecoxib 25 mg on the prevention of Alzheimer's Disease and cognitive decline in patients ≥65 years of age *with mild cognitive impairment*. Eligible patients were randomized to receive rofecoxib 25 mg or placebo for 2 years or until 220 cases of clinically diagnosed probable or possible Alzheimer's Disease were observed, whichever came later. Safety and tolerability were to be assessed at all visits. At the time of the July 12, 2001 SUR, study 078 was ongoing. Due to slow accrual, after two years the protocol had an amendment to allow duration of 4 years. However, the study was terminated earlier in April 2003, when 189 events had been reached. The sponsor considered that it would take too long to achieve 220 events and that additional events would not change the results.

Protocol 126 was similar in size and design to study 091. Since study 091 failed to show efficacy, study 126 was considered futile and terminated early, with an approximate median exposure of five months. At the time of the July 12, 2001 SUR, there were no difference in the number of CV/T events between Vioxx and placebo in this study.

All the Alzheimer's studies initially excluded patients at high cardiovascular risk taking low dose aspirin. The Sponsor later amended the protocols to allow low dose aspirin for cardiovascular prophylaxis for those patients who need it. The following are some of the exclusion criteria used in the Alzheimer's studies (protocol 078):

1 Patient with a history (within 2 years) or current evidence of major stroke, multiple lacunar infarcts or transient ischemic events.
2 Patient with a history of angina or congestive heart failure with symptoms at rest.
3 Patients with a history of myocardial infarction or coronary artery bypass grafting, angioplasty, or stent placement within 1 year prior to study start.
4 Patients taking the following medications:
    - Warfarin, heparin, ticlopidine.
    - NSAIDs (including salicylates or other aspirin-containing compounds) on a chronic basis (defined as =7 total days out of the last 30 days for 2 consecutive months prior to potential study entry).
    - Estrogen replacement therapies (excluding topical cream preparations)

2. Review of current submission of March 30, 2004

At the time of the April 2002 labeling negotiations, only Vioxx studies 078 and 091, were included in the label. These studies together had a median exposure of at least 14

months. The thought was that adding a few CV/T events from a study with shorter exposure such as study 126, could dilute the results. The current submission includes updated results of studies 078 and 091 only. This reviewer has requested additional information from studies 078, 091 and 126 individually and combined. This information is pending at the time of this review.

a. Demographics

Demographic characteristics, co-morbid conditions and concomitant medications were similar in general in both treatment groups. The studies included an elderly population (mean age 75 years, range 49 to 95 years); 60% were male and 95% were Caucasian. Approximately 6% of patients in each treatment arm used low dose aspirin.

There was a mild imbalance in the number of patients with a prior history of MI (3.1 % vs. 4.5% in the Vioxx 25 and placebo groups, respectively). Also, there was a mild imbalance in the number of patients with hyperlipidemia: 4.6% and 5.8% in the Vioxx and placebo groups, respectively. However, there were more patients with greater than one risk factor for coronary artery disease in the Vioxx group (57.5%) as compared to placebo (54.8%). It is unclear how these factors may have influenced the results related to cardiovascular outcomes.

Table 1 shows baseline cardiovascular risks factors and history of a CV/T event

Table 1. Patients with CV risk factors and history of CV/T (ITT)

Risk Factor	Rofecoxib 25 mg (N=1071)		Placebo (N=1078)	
	n	(%)	n	(%)
History of ≥1 risk factor for coronary disease	616	(57.5)	591	(54.8)
History of hypertension	407	(38.0)	361	(33.5)
History of diabetes	107	(10.0)	108	(10.0)
History of hypercholesterolemia	251	(23.4)	256	(23.7)
Current smoker	70	(6.5)	73	(6.8)
History of ≥2 risk factors for coronary disease	183	(17.1)	175	(16.2)
History of cardiovascular thrombotic event†	164	(15.3)	152	(14.1)

Source: Table 2 of s030. Although a patient may have had 2 or more secondary diagnoses, the patient is counted only once within a category. **The same patient may appear in different categories.**
† Patients with a past history of myocardial infarction, angina pectoris, angina unstable, coronary artery disease, coronary artery occlusion, coronary artery stenosis, ischemic heart disease, ventricular tachycardia, ST-segment depression, carotid artery occlusion, carotid artery stenosis, cerebral infarction, cerebrovascular accident, cerebrovascular disorder, lacunar infarction, transient ischemic attack, vertebrobasilar insufficiency, pulmonary edema, angioplasty, aortic aneurysm repair, cardiac operation, coronary bypass, endarterectomy, thromboendarterectomy, or vascular bypass graft**.**

b) Exposure data

Based on the first dose of study drug, the first patient entered the trial on 10-Feb-1999 for Protocol 091 and on 29-Apr-1998 for Protocol 078. Based on the last patient visit, the last patient completed the trial on 30-Nov-2000 for Protocol 091 and on 23-Apr-2003 for Protocol 078.

The cut-off date for the July 12, 2001, Safety Update Report of the Alzheimer's studies was March 16, 2001. Median exposure to treatment in studies 078 and 091 is presented in Table 2.

Table 2. Alzheimer's studies 078 and 091. Exposure up to March 16, 2001.

	Rofecoxib 25 mg			Placebo		
	N	Pt/years at risk	Median duration (days)	N	Pt/years at risk	Median duration (days)
091(completed)	346	301	366	346	366	448
078 (ongoing)	721	996	520	729	1098	577
	1067			1075		

Source: Sponsor's tables. SUR submitted 7/12/01 and response to request for information submitted 2/19/02.

It is unclear why the number of patients randomized to each treatment group in the July 12, 2001 submission (1067 and 1075 for Vioxx and placebo, respectively) differs from the numbers in the current submission (1069 and 1074, for Vioxx and placebo, respectively) and the number of patients in Table 2 of the ISS for s030 (1071 and 1067, respectively). A request for clarification has been sent to the Sponsor and is pending at the time of this review.

The mean duration of exposure to study drug as per the March 30, 2004 supplemental application was 539 days (19 months) and 629 days (21 months) for Vioxx and placebo, respectively for both studies combined. Information regarding the median duration of exposure in each study for each treatment group has been requested and is pending at the time of this review.

c) Safety results

1. Deaths

1.1 Total cause mortality

There were 41 and 23 deaths for all causes in the Vioxx 25 and placebo groups respectively in studies 078 and 091 combined, including on-drug deaths (Table 3.a) and deaths that occurred within 14 days off-drug (Table 3.b). Review of the causes of death did not suggest a particular pattern, with the exception of cardiovascular deaths, as noted below. A detailed review of case reports forms has not been conducted by this reviewer yet.

Table 3. Deaths in Alzheimer's studies 078 and 091 (as per March 30, 2004 submission)

Table 3.a Patients with Death in studies 078 and 091, as reported by the investigator. On-Drug population.

	Rofecoxib (N=1069)		Placebo (N=1074)	
	n	(%)	n	(%)
Patients with one or more adverse experience	36[†]	(3.4)	22[‡]	(2.0)
Blood and Lymphatic System Disorders	**1**	**(0.1)**	**0**	**(0.0)**
Hypercoagulation	1	(0.1)	0	(0.0)
Cardiac Disorders	**12**	**(1.1)**	**6**	**(0.6)**
Acute myocardial infarction	2	(0.2)	3	(0.3)
Cardiac arrest	2	(0.2)	1	(0.1)
Cardiac failure NOS	0	(0.0)	1	(0.1)
Cardio-respiratory arrest	3	(0.3)	1	(0.1)
Hypertensive heart disease	1	(0.1)	0	(0.0)
Myocardial infarction	2	(0.2)	0	(0.0)
Ventricular fibrillation	3	(0.3)	0	(0.0)
Gastrointestinal Disorders	**2**	**(0.2)**	**1**	**(0.1)**
Bowel sounds abnormal	0	(0.0)	1	(0.1)
Duodenal ulcer hemorrhage	1	(0.1)	0	(0.0)
Gastric perforation	1	(0.1)	0	(0.0)
Intestinal ischaemia	0	(0.0)	1	(0.1)
Pancreatitis NOS	0	(0.0)	1	(0.1)
General Disorders and Administration Site Conditions	**2**	**(0.2)**	**1**	**(0.1)**
Death NOS	1	(0.1)	0	(0.0)
Multi-organ failure	0	(0.0)	1	(0.1)
Sudden death	1	(0.1)	0	(0.0)
Infections and Infestations	**6**	**(0.6)**	**0**	**(0.0)**
Bronchopneumonia NOS	1	(0.1)	0	(0.0)
Empyema NOS	1	(0.1)	0	(0.0)
Endocarditis infective	1	(0.1)	0	(0.0)
Pneumonia NOS	5	(0.5)	0	(0.0)
Injury, Poisoning and Procedural Complications	**5**	**(0.5)**	**0**	**(0.0)**
Electric shock	1	(0.1)	0	(0.0)
Head injury	1	(0.1)	0	(0.0)
Poly traumatism	1	(0.1)	0	(0.0)
Post procedural complication	1	(0.1)	0	(0.0)
Traumatic chest injury NOS	1	(0.1)	0	(0.0)
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	**9**	**(0.8)**	**9**	**(0.8)**
Acute myeloid leukemia NOS	1	(0.1)	1	(0.1)
Acute myelomonocytic leukemia	0	(0.0)	1	(0.1)
Adenocarcinoma NOS	0	(0.0)	2	(0.2)
Bladder cancer NOS	0	(0.0)	1	(0.1)
Bone cancer metastatic	1	(0.1)	0	(0.0)
Chronic lymphocytic leukemia NOS	1	(0.1)	0	(0.0)
Colon cancer metastatic	0	(0.0)	1	(0.1)
Lung cancer metastatic	1	(0.1)	0	(0.0)

Lung neoplasm malignant	1	(0.1)	0	(0.0)
Lymphoma NOS	0	(0.0)	1	(0.1)
Malignant brain neoplasm NOS	1	(0.1)	0	(0.0)
Malignant melanoma	0	(0.0)	1	(0.1)
Metastases to liver	0	(0.0)	1	(0.1)
Metastatic neoplasm NOS, primary site unknown	0	(0.0)	1	(0.1)
Esophageal carcinoma NOS	1	(0.1)	0	(0.0)
Pancreatic carcinoma NOS	1	(0.1)	0	(0.0)
Pancreatic neoplasm NOS	1	(0.1)	0	(0.0)
Squamous cell carcinoma of skin	1	(0.1)	0	(0.0)
Nervous System Disorders	**1**	**(0.1)**	**3**	**(0.3)**
Cerebrovascular accident	1	(0.1)	0	(0.0)
Dementia of the Alzheimer's type NOS	0	(0.0)	1	(0.1)
Intracranial hemorrhage NOS	0	(0.0)	2	(0.2)
Renal and Urinary Disorders	**2**	**(0.2)**	**2**	**(0.2)**
Renal failure acute	1	(0.1)	0	(0.0)
Renal failure NOS	1	(0.1)	2	(0.2)
Respiratory, Thoracic, and Mediastinal Disorders	**2**	**(0.2)**	**2**	**(0.2)**
Acute respiratory failure	0	(0.0)	1	(0.1)
Chronic obstructive airways disease	0	(0.0)	1	(0.1)
Interstitial lung disease	1	(0.1)	0	(0.0)
Pulmonary fibrosis	1	(0.1)	0	(0.0)
Vascular Disorders	**1**	**(0.1)**	**2**	**(0.2)**
Aortic aneurysm rupture	0	(0.0)	1	(0.1)
Atherosclerosis	1	(0.1)	0	(0.0)
Hypertension NOS	0	(0.0)	1	(0.1)

Source. Table 11, ISS, s030.

Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. **The same patient may appear in different categories.** † This count does not include 5 patients (ANs 0290, 0536, and 1113 from Protocol 078 ; ANs 0376 and 0964 from Protocol 091) with fatal off-drug adverse experiences that may have been related to previous non-fatal, on-drug adverse experiences. ‡ This count does not include 1 patient (AN 0832) from Protocol 091 with a fatal off-drug adverse experience that may have been related to a previous non-fatal, on-drug adverse experience.

Table 3.b. Patients with Off-Drug Death possibly related to previous On-Drug adverse experiences.

Study	AN	Treatment Group	Number of Days Off Drug When AE Started	Rel Day of AE Onset	Fatal Adverse Experience (Cause of Death)	Rel Day of Death	Prior Adverse Experience[†]
078	0290	Rofecoxib 25 mg	15	594	Lung neoplasm malignant	625	Cough, bloody sputum
078	0536	Rofecoxib 25 mg	104	954	Ovarian cancer metastatic	1021	Abdominal pain
078	1113	Rofecoxib 25 mg	62	102	Acute lymphocytic leukemia	459	Decreased leukocytes
091	0376	Rofecoxib 25 mg	31	203	Fungemia	220	Esophageal burn
091	0964	Rofecoxib 25 mg	29	58	Cerebrovascular accident	58	Dizziness, nausea
091	0832	Placebo	18	479	Cardiac arrest	479	Pneumonia, atrial fibrillation

[†] Onset within 14 days after final dose of study drug.

Source: Table 12. ISS. S030.

As per Tables 3a and b, total cause mortality was greater for Vioxx 25 mg as compared to placebo.

1.2 Cardiovascular deaths (confirmed by CV adjudication committee)

Of all deaths, 11 and 5 were cardiovascular thrombotic deaths confirmed by the CV adjudication committee (See Table below) in the Vioxx and placebo groups, respectively.

Table 4. Updated listing of confirmed cardiovascular deaths in Alzheimer's Studies.

Vioxx 25 mg (n=11)	Placebo (n= 5)
Protocol 091	
1 acute MI	1 sudden cardiac death
1 sudden cardiac death	1 hemorrhagic stroke
1 ischemic stroke	1 ruptured aortic aneurysm
Protocol 078	
7 sudden cardiac death	3 sudden cardiac death
1 acute MI	1 acute MI

In addition to these deaths, there was one hemorrhagic stroke and one ruptured aortic aneurism in the placebo group, in study 091.

Although the numbers are small, there is greater number of cardiovascular thrombotic deaths in the rofecoxib 25 mg daily group, as compared to placebo. Of note, there were 8 vs. 4 cases of sudden cardiac death. The finding of more cardiovascular deaths in the Alzheimer's studies is not consistent with other studies, such as VIGOR and APPROVe, in which the number of cardiovascular deaths was the same in Vioxx as compared to naproxen (VIGOR) and Vioxx as compared to placebo.

Shift analyses of ECG changes from baseline have been requested and are pending at the time of this review.

2. Cardiovascular thrombotic events in the Alzheimer's studies

2.1 Investigator reported Serious Cardiovascular Thrombotic events

All cases of investigator reported serious cardiovascular events (within a list of pre-specified terms used by the sponsor in prior studies), as well as all deaths (cardiovascular and non-cardiovascular) were referred for evaluation by a blinded, independent, CV adjudication committee, that would confirm that the cases were indeed CV thrombotic.
This list and the number of patients with investigator reported serious CV/T events referred for adjudication has not been provided in this application.

2.1 Confirmed or Adjudicated CV/T events (including fatal and non-fatal events)

Consistent with the interim results of CV/T events submitted in July 12, 2001, the current submission of March 30, 2004, did not suggest an excess in the total number of CV thrombotic events for Vioxx as compared to placebo. In particular, there was no excess of myocardial infarction in the Vioxx group (n=14) as compared to placebo (n=14) (Table 5), but there was an excess of cerebrovascular events on placebo (n=17) as compared to Vioxx (n=7). However, mean exposure was longer for placebo patients (21 months) as compared to Vioxx (19 months). The following table includes updated confirmed cardiovascular thrombotic events from the long-term studies 078 and 091.

Table 5. Confirmed cardiovascular thrombotic events in studies 078 and 091

Endpoint Terms	MK-0966 25 mg (N=1069) 1661 Patient-Years		Placebo (N=1074) 1917 Patient-Years	
	n (%)†	Rate‡	n (%)†	Rate‡
Total number of patients with Endpoint	42 (3.93)	2.53	48 (4.47)	2.50
Cardiac Events	29 (2.71)	1.75	25 (2.33)	1.30
Acute myocardial infarction	14 (1.31)	0.84	14 (1.30)	0.73
Fatal acute myocardial infarction	2 (0.19)	0.12	1 (0.09)	0.05
Sudden cardiac death	8 (0.75)	0.48	4 (0.37)	0.21
Unstable angina pectoris	7 (0.65)	0.42	9 (0.84)	0.47
Cerebrovascular Events	14 (1.31)	0.84	20 (1.86)	1.04
Fatal ischemic cerebrovascular stroke	1 (0.09)	0.06	0 (0.00)	0.00
Ischemic cerebrovascular stroke	6 (0.56)	0.36	17 (1.58)	0.89
Transient ischemic attack	7 (0.65)	0.42	3 (0.28)	0.16
Peripheral Vascular Events	0 (0.00)	0.00	5 (0.47)	0.26
Peripheral arterial thrombosis	0 (0.00)	0.00	1 (0.09)	0.05
Peripheral venous thrombosis	0 (0.00)	0.00	3 (0.28)	0.16
Pulmonary embolism	0 (0.00)	0.00	1 (0.09)	0.05

Patient with multiple events may be counted more than once in different terms, but only once in one term.

† Crude incidence (100×n/N).

‡ Events per 100 patient-years, where patient-years at risk (PYR) were calculated based on the overall endpoint.

Source: Table 20, ISS, s030.

The finding of no difference in MI (14 in each group) but greater number of ischemic strokes in the placebo group (n=17) as compared to VIoxx (n= 7) is not consistent with VIGOR (in which there was an increase in the number of MI (20 vs. 4) but no difference in ischemic strokes (8 and 9) for Vioxx 50 and naproxen, respectively) or what observed in the APPROVe study (an excess of MI and strokes for Vioxx as compared to placebo).

(It is unclear whether the 14 acute myocardial infarctions include the fatal cases. If not, there would be 16 and 15 MIs, not a large difference. A request for additional information is pending at the time of this review)

2.3 Analyses of Confirmed CV/T events over time

Evaluation of CV/T events incidence rates over time shows that the relative risk for these events is lower on Vioxx as compared to placebo during the first 2 years but then, the incidence rate for Vioxx crosses the placebo line (Table 6 and Figure 1).

Of note, the number of patients remaining in the study after two years is relatively small for adequate evaluation of cardiovascular events (243 and 185 for Placebo and Vioxx, respectively) and there is wide overlap of the 95% confidence intervals, which hampers the interpretation of the results. At no time the differences are statistically significant.

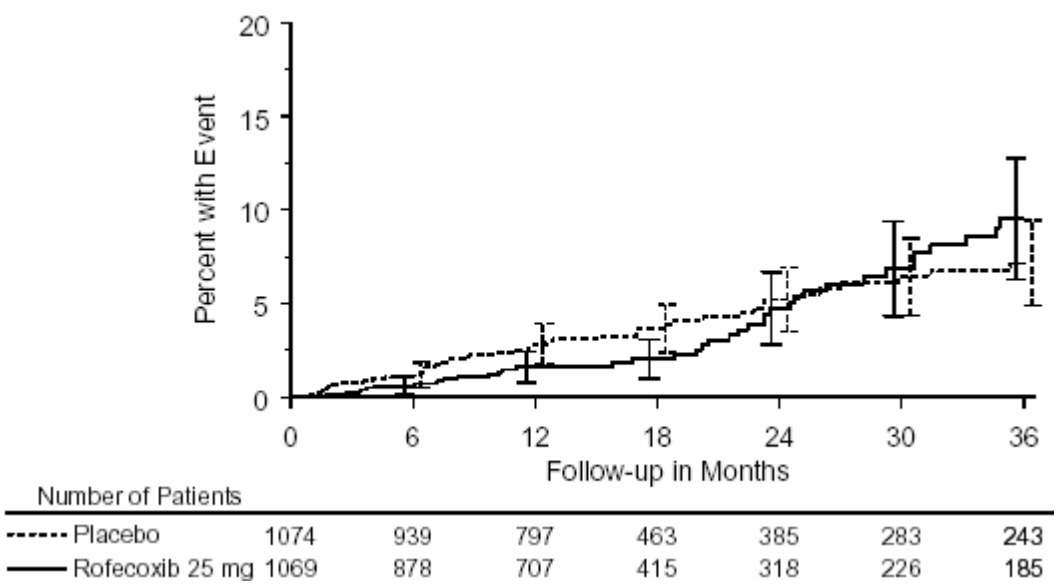
Table 6. CV/T events over time in studies 078 and 091

Time Interval	Rofecoxib			Placebo			Relative Risk‡ (95% CI)
	Number At Risk	Cases/PYR (Rate†)	95% CI	Number At Risk	Cases/PYR (Rate†)	95% CI	
0 to 6 Month	1069	6/481 (1.25)	(0.56, 2.78)	1074	12/500 (2.40)	(1.36, 4.23)	0.520 (0.195, 1.385)
6 to 12 Month	878	8/398 (2.01)	(1.01, 4.02)	939	15/433 (3.46)	(2.09, 5.75)	0.580 (0.246, 1.369)
12 to 18 Month	707	2/242 (0.83)	(0.21, 3.30)	797	5/319 (1.57)	(0.65, 3.77)	0.527 (0.102, 2.718)
18 to 24 Month	415	10/184 (5.43)	(2.92, 10.10)	463	7/214 (3.27)	(1.56, 6.86)	1.661 (0.632, 4.365)
24 to 30 Month	318	6/130 (4.62)	(2.07, 10.27)	385	4/157 (2.55)	(0.96, 6.79)	1.812 (0.511, 6.420)
30 to 36 Month	226	6/103 (5.83)	(2.62, 12.97)	283	2/132 (1.52)	(0.38, 6.06)	3.845 (0.776, 19.049)
>36 Month	185	4/121 (3.31)	(1.24, 8.81)	243	3/162 (1.85)	(0.60, 5.74)	1.785 (0.400, 7.976)

PYR = Patient-years at risk.
† Per 100 PYR.
‡ Relative Risk = Ratio of rates.

Source, Table 21. ISS. s030.

Figure 1. Kaplan Meier estimates (95% CI) of Time to Confirmed Thrombotic Event (on drug population)



Source: Figure 6. ISS, 030 submission

Of note, this finding of an increased risk of CV/T events for Vioxx 25 mg after two years as compared to placebo is not consistent with VIGOR, in which the separation between Vioxx 50 mg and naproxen started at approximately 6 weeks but was more evident after 6 months, with an increase in hazard ratio after 8 months. The finding in the Alzheimer's studies, however, is consistent with APPROVe (the colon polyp prevention study) in regards to the inflexion point for an increased CV risk. However, APPROVe showed no differences in the number of CV deaths between Vioxx 25 mg and placebo.

3. Other analyses related to cardiovascular safety

3.1 Hypertension-related AEs

As seen in the table below, there was greater use of anti hypertension medication in Vioxx 25 mg as compared to placebo. This is important, however, it is known that selective and non-selective NSAIDs are associated with fluid retention and edema as well as hypertension. The lack of a comparator NSAID in this study precludes any comparative statement.

Table 7: Number of patients with Hypertension related adverse experiences (on-drug population)

Endpoint Terms	Rofecoxib 25 mg (N=1069) 1418 Patient-Years		Placebo (N=1074) 1790 Patient-Years	
	n (%)†	Rate‡	n (%)†	Rate‡
Total number of patients with endpoint	209 (19.6)	14.74	133 (12.4)	7.43
Blood pressure diastolic increased	3 (0.28)	0.21	6 (0.56)	0.34
Blood pressure increased	52 (4.86)	3.67	32 (2.98)	1.79
Blood pressure systolic increased	4 (0.37)	0.28	3 (0.28)	0.17
Diastolic hypertension	0 (0.00)	0.00	1 (0.09)	0.06
Hypertension NOS	156 (14.6)	11.0	97 (9.03)	5.42
Labile hypertension	1 (0.09)	0.07	0 (0.00)	0.00
Systolic hypertension	1 (0.09)	0.07	0 (0.00)	0.00

Patients with multiple events may be counted more than once in different terms, but only once in each term. † Crude incidence (100 × n/N). ‡ Events per 100 patient-years, where patient-years at risk were calculated based on the overall endpoint. Source: Table 16, ISS, s030

Analyses of risk of HTN related events over time indicate a constant hazard ratio (see table below)

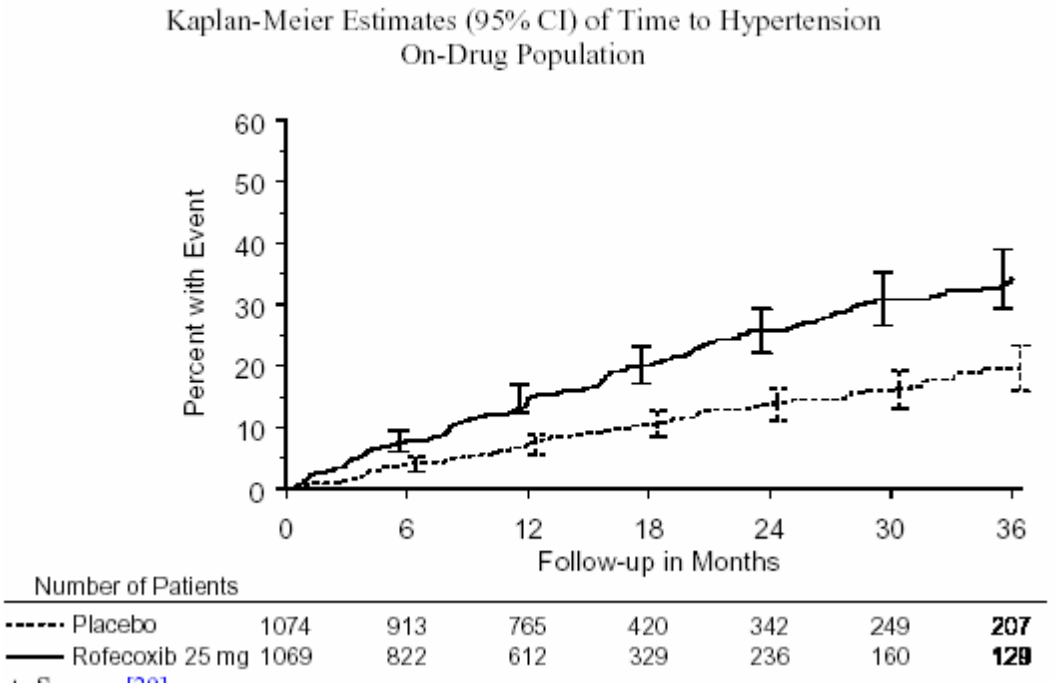
Table 8: Hypertension – Incidence rates over time (On-Drug population)

Time Interval	Rofecoxib 25 mg			Placebo			Relative Risk‡ (95% CI)
	Number At Risk	Cases/PYR (Rate†)	95% CI	Number At Risk	Cases/PYR (Rate†)	95% CI	
0 to 6 Month	1069	76/465 (16.34)	(13.05, 20.46)	1074	40/495 (8.08)	(5.93, 11.02)	2.023 (1.379, 2.966)
6 to 12 Month	822	55/362 (15.19)	(11.66, 19.79)	913	28/420 (6.67)	(4.60, 9.66)	2.279 (1.446, 3.592)
12 to 18 Month	612	26/201 (12.94)	(8.81, 19.00)	765	22/299 (7.36)	(4.84, 11.17)	1.758 (0.996, 3.102)
18 to 24 Month	329	21/139 (15.11)	(9.85, 23.17)	420	14/191 (7.33)	(4.34, 12.38)	2.061 (1.048, 4.053)
24 to 30 Month	236	13/94 (13.83)	(8.03, 23.82)	342	8/140 (5.71)	(2.86, 11.43)	2.420 (1.003, 5.839)
30 to 36 Month	160	7/75 (9.33)	(4.45, 19.58)	249	10/113 (8.85)	(4.76, 16.45)	1.055 (0.401, 2.771)
>36 Month	129	11/82 (13.41)	(7.43, 24.22)	207	11/132 (8.33)	(4.61, 15.05)	1.610 (0.698, 3.713)

PYR = Patient-years at risk.
† Per 100 PYR.
‡ Relative Risk = Ratio of rates.

Source: Table 17, ISS, s030.

Figure 2. Kaplan Meier estimates (95% CI) of time to hypertension (On-drug population)



Source: Figure 4, ISS, s030

Information on change from baseline on systolic and diastolic blood pressure in studies 078 and 091 has been requested and is pending at the time of this review.

3.2 New use of increased dosage of antianginal medication.

There was no difference in the use of antianginal medication between Vioxx and placebo in this study.

Table 9. New use of antianginal medication in 078 and 091

	Rofecoxib 25 mg (N=1069) 1653 Patient-Years		Placebo (N=1074) 1914 Patient-Years	
Endpoint Terms	n (%)†	Rate‡	n (%)†	Rate‡
Total number of patients with endpoint	35 (3.27)	2.12	34 (3.17)	1.78
Increased use	1 (0.09)	0.06	2 (0.19)	0.10
New use	34 (3.18)	2.06	33 (3.07)	1.72

Patients with multiple events may be counted more than once in different terms, but only once in each term. † Crude incidence (100 × n/N). ‡ Events per 100 patient-years, where patient-years at risk were calculated based on the overall endpoint. Source: Table 24. ISS s030.

3.3 Subgroup analyses of CV/T events in patients taking low dose ASA has been requested and is pending at the time of this review.

4. Non-cardiovascular safety

4.1 Serious adverse events

There were no differences in the total number of serious adverse events (SAE) as reported by the investigator. There were 280 (26.2%) and 305 (28.4%) cases in the Vioxx 25 and placebo groups respectively. The total number of SAE by category in general was also similar between groups. Of note, as expected, more cases of GI bleeding were observed with Vioxx as compared to placebo (see Appendix 1). Unfortunately, the study did not include a non-selective NSAID as an active comparator.

4.2 Discontinuations due to AE's

Total number of discontinuations due to adverse events was also similar among treatment groups. There were 205 (19%) and 189 (17.6%) such cases.
Evaluation by body system category shows that for some categories, such as Cardiac, GI and skin systems, there were more discontinuations from Vioxx as compared to placebo (See Appendix 2).

Of note, in the tables included in Appendix 1 and 2, patients with multiple events may be counted more than once in different terms, although only once in each term. Additionally, these tables list investigator's reported events in preferred terms (not confirmed by the GI or CV adjudication committees).

Again, the lack of a non-selective NSAID comparator precludes any statement as to whether Vioxx 25 mg is similar, better or worse than other selective and non-selective NSAIDs regarding GI, CV or skin events.

4.3 Other AE of interest

4.3.1 Fractures

Some theoretical concerns have been raised in the past regarding the possibility of impaired *healing* of fractures with NSAIDs and selective COX-2 inhibitors. The Protocol 078 and 091 combined database was searched for fracture terms. For the time-to-event analysis, only the first fracture event for each patient was considered.
There were 65 (6.1 %) patients with fractures in the rofecoxib group and 59 (5.5 %) in the placebo group (data not shown). The patient-year adjusted incidence rates were 4.05 and 3.12 per 100 patient-years for the rofecoxib and placebo groups, respectively. The overall relative risk (Vioxx over placebo) was 1.27 with 95% CI (0.89, 1.80). Of note, for the 0-6 month period, the relative risk was 1.85 (1.02, 3.35 95% CI), against Vioxx.
There were wide and overlapping CI after 6 months.

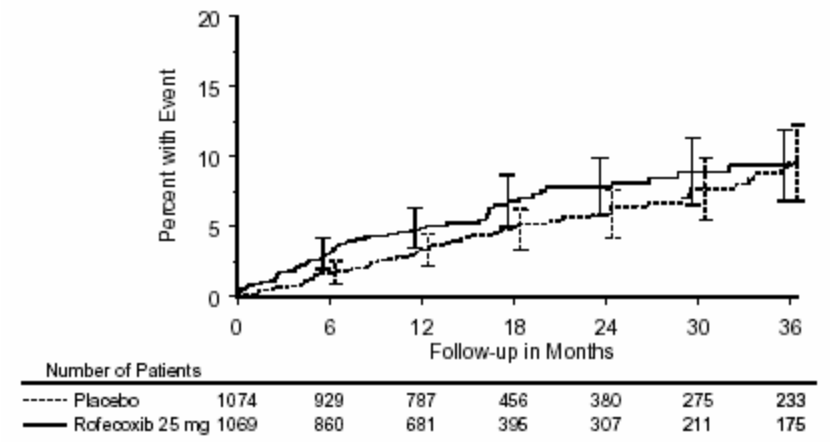
Studies 078 an 091. Updated safety. Risk of fractures overtime

Time Interval	Rofecoxib			Placebo			Relative Risk‡ (95% CI)
	Number At Risk	Cases/PYR (Rate†)	95% CI	Number At Risk	Cases/PYR (Rate†)	95% CI	
0 to 6 Month	1069	30/476 (6.30)	(4.41, 9.01)	1074	17/499 (3.41)	(2.12, 5.48)	1.850 (1.020, 3.354)
6 to 12 Month	860	15/386 (3.89)	(2.34, 6.45)	929	14/429 (3.26)	(1.93, 5.51)	1.191 (0.575, 2.467)
12 to 18 Month	681	9/232 (3.88)	(2.02, 7.46)	787	10/314 (3.18)	(1.71, 5.92)	1.218 (0.495, 2.998)
18 to 24 Month	395	4/176 (2.27)	(0.85, 6.06)	456	5/211 (2.37)	(0.99, 5.69)	0.959 (0.258, 3.572)
24 to 30 Month	307	3/122 (2.46)	(0.79, 7.62)	380	6/154 (3.90)	(1.75, 8.67)	0.631 (0.158, 2.524)
30 to 36 Month	211	1/97 (1.03)	(0.15, 7.32)	275	5/127 (3.94)	(1.64, 9.46)	0.262 (0.031, 2.241)
>36 Month	175	3/115 (2.61)	(0.84, 8.09)	233	2/155 (1.29)	(0.32, 5.16)	2.022 (0.338, 12.100)

PYR = Patient-years at risk.
† Per 100 PYR.
‡ Relative Risk = Ratio of rates.

Source: Table 29, ISS, s030.

Figure 4. KM estimates (95% CI) of time to fracture. On-drug population.



Source: Figure 10. ISS. S030.

Data from a bone mineral density study conducted by Merck (083) suggested that rofecoxib does not differ from placebo with regard to biochemical indices of bone turnover in OA patients over 3 months, and is comparable to ibuprofen 2400 mg daily after 12 months. This information would not support a true increase in the risk of fractures for Vioxx as compared to placebo, but does not answer the question whether both, ibuprofen and Vioxx have an impact on the risk of fractures as compared to placebo.

4.2 New diagnosis of Cancer

In vitro and animal data suggest that COX-2 selective inhibitors could be useful for the prevention of different kinds of cancer. At the time of Vioxx withdrawal from the market, several studies for cancer prevention were ongoing and have been stopped. Currently, several cancer prevention studies are still ongoing with Celebrex, another COX-2 selective NSAID. The Protocol 078 and 091 combined database was searched for cancer terms. For the time-to-event analysis, only the first cancer event for each patient was considered.

There were 67 (6.3%) patients with cancer in the rofecoxib group and 93 (8.7%) in the placebo group (data not shown). The patient-year adjusted incidence rates were 4.18 and 5.02 per 100 patient-years for the rofecoxib and placebo groups, respectively. The relative risk (rofecoxib over placebo) was 0.83 with 95% CI (0.61, 1.14), therefore, not statistically different.

Of note, there was some evidence for a reduced rate of basal cell carcinomas on Vioxx (1.31) versus placebo (2.10). The incidence of other types of cancers was too small to allow meaningful comparisons.

4.3 Efficacy for the prevention of progression of Alzheimers's disease (AD).

Epidemiologic data suggest that NSAIDs may have a beneficial effect in patients with AD. The efficacy of Vioxx 25 mg as compared to placebo in the prevention of progression of established AD (study 091) and in the prevention of progression to established AD in patients with Mild Cognitive Impairment (study 078) has been reviewed separately by Dr. Ranjit Mani, in the Division of Neuropharmacologic Drug Products. Vioxx failed to show efficacy in study 091 and showed a trend towards a worsening of cognitive function as compared to placebo in study 078. The Sponsor had scheduled a meeting with the FDA to further discuss these findings on September 27, 2004, but the meeting was cancelled and the drug withdrawn from the market (because of the cardiovascular findings) on September 30, 2004. This issue needs to be addressed further as it may have implications for the development of other COX-2 selective agents.

5. Summary and discussion

The Alzheimer's studies were not specifically designed or powered to address CV outcomes, however, they provided a substantial number of MI and cerebrovascular events for analyses.

Of note, the cut-off date of the data submitted to the FDA in July 12, 2001 (as part of the response to the Approvable letter for S007) was March 16, 2001. This database provided relatively long-term exposure. However, the FDA never accepted the results from the Alzheimer's studies as a replacement for prospectively designed, placebo-controlled studies. Furthermore, the FDA repeatedly requested that these data be updated, at the same time that other studies collecting placebo-controlled CV safety data were being conducted.

The updated data from the Alzheimer's studies submitted March 30, 2004, provided a mean exposure of 19 and 21 months in the Vioxx 25 and placebo groups, respectively (information on median exposure is pending at the time of this review). Again, in this updated application there was no excess of confirmed cardiovascular thrombotic events (cardiac, cerebrovascular and peripheral together) for Vioxx over placebo *overall*. Particularly, there was no excess of confirmed MI in the Vioxx 25 mg group, as compared to placebo (n= 14 in each group), and there was a greater number of confirmed ischemic strokes in placebo (n= 17) as compared to Vioxx (n= 7) . However, the number of patients exposed to placebo at the 36- month time point is someone larger than the exposure to Vioxx, which confounds the interpretation of the results.

The risk of total confirmed CV/T events over time with Vioxx appeared to be lower than placebo during the first 2 years and appeared to increase as compared to placebo after two years (Figure 1). Additionally, total cause mortality (41 vs. 23) and confirmed cardiovascular thrombotic deaths (11 and 5) were against Vioxx. This information is not entirely consistent with findings of the VIGOR and the APPROVe studies, in which there was no difference in the number of cardiovascular deaths.

The biologically plausible pro-thrombotic effect of COX-2 selective agents, plus the known effects of fluid retention, edema and hypertension associated with all NSAIDs, as well as some unknown factors may be playing a role in the detrimental cardiovascular safety profile of Vioxx as compared to placebo and naproxen.

Given the lack of information of long-term placebo-controlled studies with non-selective agents such as diclofenac and ibuprofen, the question will remain of how the cardiovascular safety profile of Vioxx would have compared to these agents.

Two additional issues that may need to be further addressed with the selective and non-selective NSAIDs are the potential for an increased risk of fractures and the potential for worsening of cognitive function in patients with mild cognitive impairment.

6. Conclusions: Based on this interim review of available data from placebo-controlled studies in patients with either established Alzheimer's disease or mild cognitive impairment as submitted by Merck on March 30, 2004, it appears that up to the time of the APPROVe study, the cardiovascular safety signal with Vioxx did not warrant a regulatory action by FDA.

Given the lack of information from long-term placebo-controlled studies with non-selective agents such as diclofenac and ibuprofen, the question will remain of how the cardiovascular safety profile of Vioxx would have compared to these agents.

Additional information and further review of adverse events from the Alzheimer's studies are pending at the time of this review.

Appendix 1. Serious Adverse Events in studies 078 and 091. Incidence ≥0.15% in one or more treatment groups. On-Drug population.

	Rofecoxib 25 mg (N=1069) 1436 Patient-Years		Placebo (N=1074) 1659 Patient-Years	
Endpoint Terms	n (%)[†]	Rate[‡]	n (%)[†]	Rate[‡]
Total number of patients	280 (26.2)	19.5	305 (28.4)	18.4
Blood and Lymphatic System Disorders	4 (0.37)	0.28	4 (0.37)	0.24
Cardiac Disorders	71 (6.64)	4.94	72 (6.70)	4.34
Acute myocardial infarction	5 (0.47)	0.35	5 (0.47)	0.30
Angina pectoris	6 (0.56)	0.42	7 (0.65)	0.42
Angina unstable	4 (0.37)	0.28	2 (0.19)	0.12
Atrial fibrillation	10 (0.94)	0.70	14 (1.30)	0.84
Atrial flutter	2 (0.19)	0.14	0 (0.00)	0.00
Atrioventricular block complete	2 (0.19)	0.14	1 (0.09)	0.06
Atrioventricular block second degree	2 (0.19)	0.14	0 (0.00)	0.00
Bradycardia NOS	3 (0.28)	0.21	5 (0.47)	0.30
Cardiac arrest	3 (0.28)	0.21	2 (0.19)	0.12
Cardiac failure congestive	9 (0.84)	0.63	15 (1.40)	0.90
Cardio-respiratory arrest	3 (0.28)	0.21	1 (0.09)	0.06
Coronary artery disease NOS	19 (1.78)	1.32	15 (1.40)	0.90
Coronary artery occlusion	1 (0.09)	0.07	2 (0.19)	0.12
Myocardial infarction	16 (1.50)	1.11	16 (1.49)	0.96
Pericardial effusion	2 (0.19)	0.14	0 (0.00)	0.00
Sick sinus syndrome	2 (0.19)	0.14	1 (0.09)	0.06
Supraventricular tachycardia	3 (0.28)	0.21	4 (0.37)	0.24
Tachycardia NOS	2 (0.19)	0.14	1 (0.09)	0.06
Ventricular fibrillation	3 (0.28)	0.21	0 (0.00)	0.00
Ventricular tachycardia	1 (0.09)	0.07	3 (0.28)	0.18
Gastrointestinal Disorders	42 (3.93)	2.92	27 (2.51)	1.63
Abdominal pain NOS	4 (0.37)	0.28	0 (0.00)	0.00
Constipation	1 (0.09)	0.07	2 (0.19)	0.12
Diarrhea NOS	4 (0.37)	0.28	0 (0.00)	0.00
Diverticulitis NOS	2 (0.19)	0.14	3 (0.28)	0.18
Diverticulum NOS	3 (0.28)	0.21	1 (0.09)	0.06
Diverticulum intestinal	2 (0.19)	0.14	1 (0.09)	0.06
Diverticulum intestinal haemorrhagica	3 (0.28)	0.21	0 (0.00)	0.00
Duodenal ulcer hemorrhage	2 (0.19)	0.14	0 (0.00)	0.00
Gastric ulcer	3 (0.28)	0.21	0 (0.00)	0.00
Gastric ulcer hemorrhage	2 (0.19)	0.14	1 (0.09)	0.06
Gastrointestinal hemorrhage NOS	5 (0.47)	0.35	1 (0.09)	0.06
Hemorrhoidal hemorrhage	2 (0.19)	0.14	0 (0.00)	0.00
Intestinal perforation NOS	0 (0.00)	0.00	2 (0.19)	0.12
Lower gastrointestinal hemorrhage	4 (0.37)	0.28	2 (0.19)	0.12
Mallory-Weiss syndrome	2 (0.19)	0.14	0 (0.00)	0.00
Nausea	2 (0.19)	0.14	1 (0.09)	0.06
Pancreatitis NOS	0 (0.00)	0.00	2 (0.19)	0.12
Rectal hemorrhage	2 (0.19)	0.14	1 (0.09)	0.06
Small intestinal obstruction NOS	3 (0.28)	0.21	1 (0.09)	0.06
Vomiting NOS	4 (0.37)	0.28	3 (0.28)	0.18
General Disorders and Administration Site Conditions	**16 (1.50)**	**1.11**	**17 (1.58)**	**1.02**
Asthenia	4 (0.37)	0.28	3 (0.28)	0.18
Chest discomfort	2 (0.19)	0.14	0 (0.00)	0.00
Chest pain	8 (0.75)	0.56	11 (1.02)	0.66
Hepatobiliary Disorders	**2 (0.19)**	**0.14**	**5 (0.47)**	**0.30**
Bile duct stone	0 (0.00)	0.00	2 (0.19)	0.12
Cholelithiasis	1 (0.09)	0.07	3 (0.28)	0.18
Immune System Disorders	**2 (0.19)**	**0.14**	**0 (0.00)**	**0.00**
Infections and Infestations	**30 (2.81)**	**2.09**	**40 (3.72)**	**2.41**
Cellulitis	5 (0.47)	0.35	5 (0.47)	0.30
Gastroenteritis NOS	2 (0.19)	0.14	1 (0.09)	0.06
Labyrinthitis NOS	0 (0.00)	0.00	2 (0.19)	0.12
Lobar pneumonia NOS	0 (0.00)	0.00	2 (0.19)	0.12
Pneumonia NOS	15 (1.40)	1.04	16 (1.49)	0.96
Pyelonephritis NOS	2 (0.19)	0.14	0 (0.00)	0.00
Urinary tract infection NOS	0 (0.00)	0.00	4 (0.37)	0.24

Urosepsis	0 (0.00)	0.00	2 (0.19)	0.12
Viral infection NOS	0 (0.00)	0.00	2 (0.19)	0.12
Injury, Poisoning and Procedural Complications	**27 (2.53)**	**1.88**	**38 (3.54)**	**2.29**
Fall	0 (0.00)	0.00	2 (0.19)	0.12
Femur fracture	0 (0.00)	0.00	3 (0.28)	0.18
Hip fracture	10 (0.94)	0.70	7 (0.65)	0.42
Rib fracture	3 (0.28)	0.21	3 (0.28)	0.18
Upper limb fracture NOS	2 (0.19)	0.14	1 (0.09)	0.06
Wrist fracture	2 (0.19)	0.14	1 (0.09)	0.06
Investigations	**1 (0.09)**	**0.07**	**2 (0.19)**	**0.12**
Metabolism and Nutrition Disorders	**6 (0.56)**	**0.42**	**6 (0.56)**	**0.36**
Dehydration	6 (0.56)	0.42	4 (0.37)	0.24
Musculoskeletal and Connective Tissue Disorders	**17 (1.59)**	**1.18**	**10 (0.93)**	**0.60**
Arthralgia	3 (0.28)	0.21	3 (0.28)	0.18
Intervertebral disc herniation	3 (0.28)	0.21	0 (0.00)	0.00
Localized osteoarthritis	2 (0.19)	0.14	3 (0.28)	0.18
Rotator cuff syndrome	2 (0.19)	0.14	0 (0.00)	0.00
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	**69 (6.45)**	**4.81**	**98 (9.12)**	**5.91**
Adenocarcinoma NOS	0 (0.00)	0.00	2 (0.19)	0.12
Basal cell carcinoma	20 (1.87)	1.39	39 (3.63)	2.35
Bladder cancer NOS	2 (0.19)	0.14	3 (0.28)	0.18
Bowen's disease	1 (0.09)	0.07	2 (0.19)	0.12
Breast cancer NOS	4 (0.37)	0.28	4 (0.37)	0.24
Colon cancer NOS	1 (0.09)	0.07	2 (0.19)	0.12
Lung neoplasm malignant	2 (0.19)	0.14	5 (0.47)	0.30
Malignant melanoma	2 (0.19)	0.14	2 (0.19)	0.12
Esophageal carcinoma NOS	1 (0.09)	0.07	2 (0.19)	0.12
Prostate cancer NOS	16 (1.50)	1.11	16 (1.49)	0.96
Prostate cancer recurrent	1 (0.09)	0.07	2 (0.19)	0.12
Squamous cell carcinoma of skin	12 (1.12)	0.84	17 (1.58)	1.02
Nervous System Disorders	**55 (5.14)**	**3.83**	**64 (5.96)**	**3.86**
Abasia	0 (0.00)	0.00	2 (0.19)	0.12
Carotid artery occlusion	1 (0.09)	0.07	2 (0.19)	0.12
Carotid artery stenosis	1 (0.09)	0.07	8 (0.74)	0.48
Cerebrovascular accident	11 (1.03)	0.77	15 (1.40)	0.90
Dizziness	4 (0.37)	0.28	2 (0.19)	0.12
Intracranial hemorrhage NOS	1 (0.09)	0.07	2 (0.19)	0.12
Metabolic encephalopathy NOS	0 (0.00)	0.00	2 (0.19)	0.12
Spinal stenosis NOS	4 (0.37)	0.28	1 (0.09)	0.06
Syncope	13 (1.22)	0.91	13 (1.21)	0.78
Transient Ischaemic attack	11 (1.03)	0.77	9 (0.84)	0.54
Psychiatric Disorders	**11 (1.03)**	**0.77**	**12 (1.12)**	**0.72**
Agitation	2 (0.19)	0.14	2 (0.19)	0.12
Confusional state	3 (0.28)	0.21	1 (0.09)	0.06
Depression	2 (0.19)	0.14	1 (0.09)	0.06
Mental status changes	1 (0.09)	0.07	2 (0.19)	0.12
Psychotic disorder NOS	1 (0.09)	0.07	2 (0.19)	0.12
Renal and Urinary Disorders	**14 (1.31)**	**0.97**	**10 (0.93)**	**0.60**
Calculus bladder	2 (0.19)	0.14	0 (0.00)	0.00
Hematuria	3 (0.28)	0.21	1 (0.09)	0.06
Renal failure NOS	4 (0.37)	0.28	2 (0.19)	0.12
Renal impairment NOS	2 (0.19)	0.14	1 (0.09)	0.06
Urinary retention	1 (0.09)	0.07	2 (0.19)	0.12
Reproductive System and Breast Disorders	**5 (0.47)**	**0.35**	**10 (0.93)**	**0.60**
Benign prostatic hyperplasia	4 (0.37)	0.28	6 (0.56)	0.36
Prostatic hypertrophy	0 (0.00)	0.00	2 (0.19)	0.12
Respiratory, Thoracic and Mediastinal Disorders	**21 (1.96)**	**1.46**	**15 (1.40)**	**0.90**
Aspiration	0 (0.00)	0.00	2 (0.19)	0.12
Asthma NOS	2 (0.19)	0.14	1 (0.09)	0.06
Bronchitis NOS	3 (0.28)	0.21	2 (0.19)	0.12
Chronic obstructive airways disease	5 (0.47)	0.35	2 (0.19)	0.12
Pleural effusion	2 (0.19)	0.14	1 (0.09)	0.06
Pulmonary embolism	2 (0.19)	0.14	1 (0.09)	0.06
Respiratory distress	0 (0.00)	0.00	3 (0.28)	0.18
Respiratory failure	1 (0.09)	0.07	2 (0.19)	0.12
Skin and Subcutaneous Tissue Disorders	**2 (0.19)**	**0.14**	**0 (0.00)**	**0.00**
Vascular Disorders	**6 (0.56)**	**0.42**	**12 (1.12)**	**0.72**
Deep vein thrombosis	0 (0.00)	0.00	3 (0.28)	0.18
Hypertension NOS	2 (0.19)	0.14	3 (0.28)	0.18

Patients with multiple events may be counted more than once in different terms, but only once in each term.
† Crude incidence (100 × n/N). ‡ Events per 100 patient-years, where patient-years at risk were calculated based on the overall endpoint.

Source Table 9. ISS. S030.

Appendix 2. Patients with Discontinuations due to Adverse Events in studies 078 and 091 (investigator's terms). Incidence ≥ 0.15%. On Drug population.

	Rofecoxib 25 mg (N=1069) 1652 Patient-Years		Placebo (N=1074) 1935 Patient-Years	
Endpoint Terms	n (%)†	Rate‡	n (%)†	Rate‡
Total number of patients with endpoint	205 (19.2)	12.41	189 (17.6)	9.77
Blood and Lymphatic System Disorders	**4 (0.37)**	**0.24**	**6 (0.56)**	**0.31**
Anemia NOS	3 (0.28)	0.18	6 (0.56)	0.31
Cardiac Disorders	**29 (2.71)**	**1.76**	**15 (1.40)**	**0.78**
Acute myocardial infarction	4 (0.37)	0.24	3 (0.28)	0.16
Angina unstable	2 (0.19)	0.12	0 (0.00)	0.00
Atrial fibrillation	2 (0.19)	0.12	0 (0.00)	0.00
Bradycardia NOS	0 (0.00)	0.00	2 (0.19)	0.10
Cardiac arrest	3 (0.28)	0.18	1 (0.09)	0.05
Cardiac failure congestive	4 (0.37)	0.24	2 (0.19)	0.10
Cardio-respiratory arrest	2 (0.19)	0.12	1 (0.09)	0.05
Coronary artery disease NOS	5 (0.47)	0.30	4 (0.37)	0.21
Myocardial infarction	5 (0.47)	0.30	3 (0.28)	0.16
Ventricular fibrillation	3 (0.28)	0.18	0 (0.00)	0.00
Ear and Labyrinth Disorders	**2 (0.19)**	**0.12**	**5 (0.47)**	**0.26**
Tinnitus	2 (0.19)	0.12	1 (0.09)	0.05
Vertigo	1 (0.09)	0.06	3 (0.28)	0.16
Eye Disorders	**3 (0.28)**	**0.18**	**1 (0.09)**	**0.05**
Macular degeneration	2 (0.19)	0.12	0 (0.00)	0.00
Gastrointestinal Disorders	**45 (4.21)**	**2.72**	**28 (2.61)**	**1.45**
Abdominal discomfort	2 (0.19)	0.12	1 (0.09)	0.05
Abdominal distension	2 (0.19)	0.12	1 (0.09)	0.05
Abdominal pain NOS	4 (0.37)	0.24	2 (0.19)	0.10
Constipation	1 (0.09)	0.06	2 (0.19)	0.10
Diarrhea NOS	8 (0.75)	0.48	2 (0.19)	0.10
Duodenal ulcer	2 (0.19)	0.12	0 (0.00)	0.00
Dyspepsia	4 (0.37)	0.24	4 (0.37)	0.21
Gastric ulcer	4 (0.37)	0.24	0 (0.00)	0.00
Gastritis NOS	4 (0.37)	0.24	1 (0.09)	0.05
Gastrointestinal hemorrhage NOS	3 (0.28)	0.18	0 (0.00)	0.00
Gastroesophageal reflux disease	2 (0.19)	0.12	2 (0.19)	0.10
Mallory-Weiss syndrome	2 (0.19)	0.12	0 (0.00)	0.00
Nausea	6 (0.56)	0.36	5 (0.47)	0.26
Upper gastrointestinal hemorrhage	2 (0.19)	0.12	0 (0.00)	0.00
Vomiting NOS	2 (0.19)	0.12	4 (0.37)	0.21
General Disorders and Administration Site Conditions	**17 (1.59)**	**1.03**	**14 (1.30)**	**0.72**
Asthenia	2 (0.19)	0.12	4 (0.37)	0.21
Chest pain	3 (0.28)	0.18	4 (0.37)	0.21
Gait abnormal	2 (0.19)	0.12	0 (0.00)	0.00
Edema peripheral	4 (0.37)	0.24	0 (0.00)	0.00
Infections and Infestations	**11 (1.03)**	**0.67**	**5 (0.47)**	**0.26**

Pneumonia NOS	4 (0.37)	0.24	0 (0.00)	0.00
Injury, Poisoning and Procedural Complications	**6 (0.56)**	**0.36**	**9 (0.84)**	**0.47**
Hip fracture	1 (0.09)	0.06	2 (0.19)	0.10
Rib fracture	0 (0.00)	0.00	2 (0.19)	0.10
Investigations	**8 (0.75)**	**0.48**	**3 (0.28)**	**0.16**
Blood pressure increased	4 (0.37)	0.24	3 (0.28)	0.16
Fecal occult blood positive	3 (0.28)	0.18	0 (0.00)	0.00
Metabolism and Nutrition Disorders	**6 (0.56)**	**0.36**	**2 (0.19)**	**0.10**
Dehydration	4 (0.37)	0.24	1 (0.09)	0.05
Fluid retention	2 (0.19)	0.12	0 (0.00)	0.00
Musculoskeletal and Connective Tissue Disorders	**17 (1.59)**	**1.03**	**30 (2.79)**	**1.55**
Arthralgia	3 (0.28)	0.18	7 (0.65)	0.36
Arthritis NOS	3 (0.28)	0.18	7 (0.65)	0.36
Back pain	4 (0.37)	0.24	2 (0.19)	0.10
Localized osteoarthritis	0 (0.00)	0.00	3 (0.28)	0.16
Osteoarthritis NOS	2 (0.19)	0.12	8 (0.74)	0.41
Pain in extremity	3 (0.28)	0.18	0 (0.00)	0.00
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	**7 (0.65)**	**0.42**	**19 (1.77)**	**0.98**
Bladder cancer NOS	0 (0.00)	0.00	2 (0.19)	0.10
Lung neoplasm malignant	0 (0.00)	0.00	4 (0.37)	0.21
Esophageal carcinoma NOS	1 (0.09)	0.06	2 (0.19)	0.10
Nervous System Disorders	**33 (3.09)**	**2.00**	**28 (2.61)**	**1.45**
Cerebrovascular accident	7 (0.65)	0.42	6 (0.56)	0.31
Dizziness	5 (0.47)	0.30	5 (0.47)	0.26
Headache	2 (0.19)	0.12	3 (0.28)	0.16
Intracranial hemorrhage NOS	1 (0.09)	0.06	2 (0.19)	0.10
Somnolence	2 (0.19)	0.12	0 (0.00)	0.00
Syncope	3 (0.28)	0.18	3 (0.28)	0.16
Transient Ischemic attack	4 (0.37)	0.24	2 (0.19)	0.10
Psychiatric Disorders	**11 (1.03)**	**0.67**	**18 (1.68)**	**0.93**
Agitation	1 (0.09)	0.06	3 (0.28)	0.16
Confusional state	2 (0.19)	0.12	4 (0.37)	0.21
Depression	3 (0.28)	0.18	2 (0.19)	0.10
Renal and Urinary Disorders	**9 (0.84)**	**0.54**	**5 (0.47)**	**0.26**
Renal Failure NOS	6 (0.56)	0.36	1 (0.09)	0.05
Urinary retention	0 (0.00)	0.00	2 (0.19)	0.10
Respiratory, Thoracic and Mediastinal Disorders	**8 (0.75)**	**0.48**	**6 (0.56)**	**0.31**
Dyspnea	4 (0.37)	0.24	0 (0.00)	0.00
Pulmonary fibrosis	2 (0.19)	0.12	0 (0.00)	0.00
Skin and Subcutaneous Tissue Disorders	**11 (1.03)**	**0.67**	**4 (0.37)**	**0.21**
Pruritus	3 (0.28)	0.18	1 (0.09)	0.05
Rash NOS	6 (0.56)	0.36	2 (0.19)	0.10
Vascular Disorders	**15 (1.40)**	**0.91**	**11 (1.02)**	**0.57**
Hypertension NOS	11 (1.03)	0.67	7 (0.65)	0.36

Patients with multiple events may be counted more than once in different terms, but only once in each term. † Crude incidence (100 × n/N).

‡ Events per 100 patient-years, where patient-years at risk were calculated based on the overall endpoint.

Source. Table 14. ISS. S030.